Proposed Decision Memo for Artificial Hearts (CAG-00322N)

Decision Summary

CMS proposes that the evidence is inadequate to conclude that the use of an artificial heart is reasonable and necessary under 1862(a)(1)(A) of the Social Security Act. CMS proposes, however, that evidence is promising for the use of artificial hearts and supports additional research for these devices under 1862(a)(1)(E) (consistent with section 1142 of the Act). Therefore, CMS proposes that the artificial heart will be covered by Medicare when performed under Coverage with Evidence Development when a clinical study meets all of the criteria listed below.

The clinical study must address at least one of the following questions:

- Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?
- What will be the average time to device failure when the device is made available to larger numbers of patients?
- Do results adequately give a reasonable indication of the full range of outcomes (both positive and negative) that might be expected from more wide spread use?

The clinical study must meet all of the following criteria:

- The study must be reviewed and approved by the Food and Drug Administration.
- The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.
- The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.
- The research study does not unjustifiably duplicate existing studies.
- The research study design is appropriate to answer the research question being asked in the study.
- The research study is sponsored by an organization or individual capable of executing the proposed study successfully.
- The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is FDA-regulated it also must be in compliance with 21 CFR Parts 50 and 56.
- All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).
- The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements for CSP or CED coverage.
- The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR § 312.81(a) and the patient has no other viable treatment options.
- The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.
- The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.

- The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.
- The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

Proposed revisions to sections 20.9 and 260.9 of the NCD Manual are available in Appendix C.

We are requesting public comments on this proposed determination pursuant to section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

Back to Top

Proposed Decision Memo

TO: Administrative File: CAG 00322N
Artificial Hearts

FROM:

Steve E. Phurrough, MD, MPA
Director, Coverage and Analysis Group

Marcel E. Salive, MD, MPH
Director, Division of Medical and Surgical Services

JoAnna Baldwin, MS
Lead Analyst

Madeline Ulrich, MD, MS
Lead Medical Officer

SUBJECT: Proposed Coverage Decision Memorandum for Artificial Hearts
DATE: February 1, 2008

I. Proposed Decision

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II. Background

Heart failure affects more than 5 million patients in the United States with 550,000 new cases each year. It is the direct cause of more than 55,000 deaths annually. It is a progressive disease which is medically managed at all stages, but which over time leads to continued deterioration in the heart's ability to pump sufficient amounts of adequately oxygenated blood. The left side of the heart pumps oxygenated blood from the lungs into the aorta for circulation throughout the body. The right side of the heart pumps blood returning from systemic circulation into the lungs for oxygenation. If the left ventricle is failing, an inadequate amount of blood will be pumped through the systemic circulation. If the right side of the heart fails, blood may back up in the circulation causing congestion in the liver, gastrointestinal tract and limbs and/or failure to provide an adequate supply of blood to the lungs to be oxygenated. Generally the cause of right-sided heart failure is longstanding left-sided failure. When optimal medical management becomes inadequate to continue to support the patient, his heart failure would be considered to be the end stage of the disease and the only remaining treatment options are a heart transplant or mechanical circulatory support. An artificial heart has been used only for severe failure of both ventricles.

Relatively small numbers of patients suffer from biventricular failure; however, exact numbers of such patients are unavailable. There are about 4000 patients approved and waiting to receive heart transplants in the United States at any one time; but only about 2000 hearts per year are transplanted due to a scarcity of donated organs. Many Medicare patients cannot qualify as heart transplant candidates due to their advanced age and/or chronic comorbid conditions.

There are a number of different mechanical devices which may be used to support the ventricles of a failing heart on either a temporary or permanent basis. Devices may be placed externally and used on a short term basis to aid recovery from an acute event such as heart surgery. When it appears the patient will require longer term support, the device is generally implanted and may be considered either as a *bridge* to recovery or *bridge* to transplantation. Sometimes a patient's prognosis is uncertain and with device support the heart may recover function. When recovery is not likely, the patient may qualify as a transplant candidate and require mechanical circulatory support until a donor heart becomes available. Ventricular assist devices (VADs), which are commonly used to supply this support, are surgically attached to, but do not replace the native ventricles.

Patients with end stage heart failure, who cannot qualify as heart transplant candidates, may in some instances obtain permanent circulatory support through the use of assistive circulatory devices such as VADs. In these cases it is expected that the patient will be supported by the device for the remainder of life and the implantation of a device in such situations is referred to as *destination* therapy.

VADs may be used alone to support the pumping action of either the right or left ventricle or in a pair to support both ventricles. The use of two VADs to support both sides of the failing heart has had limited success primarily due to relatively low pump capacity and flow when compared with a normally functioning native heart. Reduced flow fails to adequately support major organs such as kidney, liver and lungs; may cause an unsupported ventricle to fail; and may allow the patient's condition to continue to deteriorate over time.

The devices under consideration in this memorandum are biventricular replacement devices, also termed "artificial hearts." During the implantation of an artificial heart, a substantial part, including both ventricles, of the native heart is removed. The artificial heart differs from a VAD which is attached to the intact native heart at the ventricle. When the heart remains intact it remains possible for the native heart to recover its function after being assisted by a VAD. Since the artificial heart requires the resection of the ventricles, the native heart is no longer intact and such recovery is not possible. The designation "artificial heart" is somewhat of a misnomer since some portion of the native heart remains and there is no current mechanical device which fully replaces all four chambers of the heart. Over time better descriptive language for these devices may be adopted.

III. History of Medicare Coverage

In 1986, CMS explicitly noncovered the use of artificial hearts under the Medicare program. Currently, language related to artificial hearts appears in two National Coverage Determinations (NCDs). These current policies are available in their entirety in Appendix B.

NCD for Heart Transplants (Manual 100-03, Section 260.9)

F. Artificial Hearts
Medicare does not cover the use of artificial hearts as a permanent replacement for a human heart or as a temporary life-support system until a human heart becomes available for transplant (often referred to as a "bridge to transplant"). Medicare does cover a ventricular assist device (VAD) when used in conjunction with specific criteria listed in §20.9 of the NCD Manual.

NCD for Artificial Hearts and Related Devices (Manual 100-03, Section 20.9)

C. Nationally Non-Covered Indications (effective for services performed on or after May 19, 1986)
1. Artificial Heart
Since there is no authoritative evidence substantiating the safety and effectiveness of a VAD used as a replacement for the human heart, Medicare does not cover this device when used as an artificial heart.

On August 1, 2007, CMS began a national coverage determination process for artificial hearts. In a request submitted by SynCardia Systems, Inc., the agency was asked to reconsider the longstanding noncoverage policy on the use of artificial hearts. SynCardia has requested Medicare coverage for artificial hearts when used for bridge to transplantation in accordance with the Food and Drug Administration (FDA) labeled indication for their device.

CMS determined that a broader analysis of the use of artificial hearts is appropriate since a second such device has received approval from the FDA for humanitarian use as destination therapy for patients in end stage biventricular failure, who cannot qualify as transplant candidates. Therefore, this proposed decision memorandum includes an analysis of implantation of artificial hearts for both destination therapy and bridge to transplantation.

Artificial hearts fall under the benefit categories of Inpatient Hospital Services and Prosthetic Device (§§1861(b)(2) and 1861(s)(8) of the Social Security Act, respectively).

IV. Timeline of Recent Activities

Date	Action
August 1, 2007	CMS opens National Coverage Analysis for artificial hearts based on request submitted by SynCardia Systems, Inc. Initial 30-day public comment period begins and CMS specifically requests that commenters focus on medical evidence, physician training/requirements and hospital training/requirements.
August 31, 2007	Initial 30-day public comment period ends. CMS receives 26 comments.

V. FDA Status

Currently two artificial hearts are FDA approved and are required by that agency to undergo post-approval studies.

Approval via Premarket Approval (PMA) application
SynCardia CardioWest temporary Total Artificial Heart (TAH-t)
(http://www.fda.gov/cdrh/PDF3/p030011b.pdf)
FDA Approval Date: October 15, 2004
Indications for Use: The SynCardia Systems, Inc., CardioWest temporary Total Artificial Heart (hereinafter called the TAH-t) is indicated for use as a bridge to transplantation in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. The CardioWest TAH-t System is intended for use inside the hospital.

FDA required a post-approval study of at least 50 patients to be followed for at least one year, "to provide necessary assurance that the success of the device at one center can be reproduced at different centers." The endpoints of the study are to include, but were not limited to "survival to transplant, adverse events, device malfunction." That study is currently underway.

PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Due to the level of risk associated with Class III devices, FDA has determined that general and special controls alone are insufficient toestablish a reasonableassuranceofsafety and effectiveness. Therefore, these devices require a premarket approval (PMA) application under section 515 of the Food Drug and Cosmetic Act in order to obtain marketing clearance.

PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device.

Approval via Humanitarian Device Exemption (HDE) application
AbioCor Implantable Replacement Heart

(http://www.fda.gov/cdrh/pdf4/H040006b.pdf)
FDA Approval Date: September 5, 2006
Indications for Use: The AbioCor® is indicated for use in severe biventricular end stage heart disease patients who are not cardiac transplant candidates and who
- are less than 75 years old,
- require multiple inotropic support[1],
- are not treatable by LVAD destination therapy, and
- cannot be weaned from biventricular support if on such support.

FDA required a post-approval study "to follow the first twenty-five patients implanted…until death (while on the device) or other outcome (e.g. elective termination by family, device malfunction, etc.)."

Since 1990, Congress has required the FDA to approve certain devices that are designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States. FDA categorizes these devices as Humanitarian Use Devices (HUD) and may provide a Humanitarian Device Exemption (HDE) that allows the device to be marketed for the limited condition. In order for the FDA to authorize the marketing of an HUD, the device manufacturer must submit an HDE application which has some similarity to a pre-market approval (PMA) application, but need not present clinical data addressing the effectiveness of the device. Through the review of the application and information provided, the FDA must be able "to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment" (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm). In addition, the manufacturer must show that no comparable devices are available for treatment or diagnosis of the disease or condition, and there are no other means by which the device may be brought to market (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm). The device can have other indications and the affected population can be a small subset of a disease or condition. The HDE holder is required to ensure that an HUD approved device is only used in facilities having an Institutional Review Board (IRB) that continually reviews and approves the use of this device. In addition, the amount charged for the device cannot exceed the costs of the device's research, development, fabrication, and distribution. Finally, the FDA can require annual reports of the number of devices used to determine continued HUD status.

VI. General Methodological Principles

When making national coverage decisions, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment question(s) can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

The evidence for the two FDA approved artificial heart indications will be considered separately.

Because two devices are approved for different patient populations, CMS has somewhat different outcomes of interest for each device. Outcomes of interest for both devices include patient survival, the ability to discharge the patient to home, successful device implantation and freedom from the negative effects of adverse events (e.g., device failure, infection, bleeding or neurological complications). Additionally, in the case of the SynCardia device the ultimate desired outcome is a successful heart transplant and the potential that offers for cure from heart failure. For the AbioCor device, since the patient is not expected to ever become a transplant candidate, the desired outcome is prolongation of life and discharge to home.

This National Coverage Analysis (NCA) focuses on the following question:

Is the evidence adequate to conclude that the artificial heart improves health outcomes in patients with end-stage, bi-ventricular heart failure?

B. Discussion of evidence reviewed

The CardioWest TAH-t is FDA approved as a bridge to transplant. While the patient population is in severe biventricular Class IV heart failure, they meet requirements to be listed for a heart transplant. With successful implantation of the artificial heart and appropriate care until a donor heart becomes available, they would be expected to achieve long-term survival following transplant. Thus, the outcomes with which we are concerned for this population are a successful artificial heart implantation, survival to a successful transplant and continued survival thereafter without negative effects from adverse events such as device failure, infections, excessive bleeding or neurological consequences.

The AbioCor device is FDA approved for destination therapy for patients who are not candidates for heart transplantation and are near death from end stage biventricular Class IV heart failure. These patients have exhausted all other treatment options and the purpose of the artificial heart is to prolong their lives and hopefully permit meaningful quality of life (e.g., discharge from hospital to home). The outcomes of interest for this group are increased survival, discharge home and a successful implantation of the artificial heart without such adverse events as device failure, infection, excessive bleeding or neurological consequences. Since the mean length of survival for these patients thus far has been 4.5 months, improving that duration and assuring that most patients are discharged to home are important outcomes.

1. Literature Search

CMS searched PubMed using the search term “artificial heart”. The search was restricted to articles published in core clinical journals in the last 10 years (1997 to present), human trials with adult subjects older than 18 years of age, randomized clinical trials, meta-analysis and available in the English language. Our search yielded a potential of 56 articles. After restricting articles to those presenting only original clinical trial data related specifically to artificial hearts, only two articles were left for review. Excluded articles included those dealing with ventricular assist devices or other cardiac devices, drug therapies or surgical procedures for heart failure, and the physiology of heart failure.

Two documents were reviewed:

Copeland, JK, Smith, RG, Arabia, FA, et al. Cardiac replacement with a total artificial heart as a bridge to transplantation. N Eng J Med 351(9):859-67, 2004.
This is the publication of the data for the pivotal trial of the SynCardia TAH-t which served as the basis for the FDA PMA approval of this device. These data are available online at the FDA website in the Summary of Safety and Effectiveness, which we quote extensively.

Dowling, RD, Gray, LA Jr, Etoch, SW, et al. The AbioCor implantable replacement heart. Ann Thorac Surg 75(6 Suppl):S93-9.
This is a report of results from the AbioCor trial which was the basis on which FDA granted HDE approval for this device. The data are available in the FDA Summary of Safety and Probable Benefit which we reviewed extensively in our analysis.

2. External Technology Assessments

No external technology assessments were located or commissioned for this subject.

3. Internal Technology Assessment

A. SynCardia CardioWest Total Artificial Heart (TAH-t) for bridge to transplantation

In 1993, SynCardia began a non-randomized, multi-center Investigational Device Exemption (IDE) (G920101) trial of the CardioWest TAH-t with both historical and concurrent controls. The following material is excerpted from the description of that trial found at: http://www.fda.gov/cdrh/PDF3/P030011b.pdf, supplemented by details received from the requestor in response to specific inquiries by CMS for additional data.

This implantable, pulsatile device consists of two artificial ventricles made of semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood chamber from the air chamber. The diaphragms allow the ventricles to fill and eject blood when compressed by air from the external drive console. The maximum stroke volume of each ventricle is 70 ml, generating a flow rate up to 9.5 l/min. A driveline conduit for each ventricle is tunneled through the chest and attached to seven-foot drivelines that connect back to the external drive console. The controller housed in the console supplies pulses of pneumatic pressure to the drivelines connected to the ventricles. Back up air tanks and power and console batteries are automatically activated if external compressed air and/or AC power are interrupted. This console may be used only in the hospital.

Participants in this trial were transplant candidates who were at risk of imminent death from biventricular failure. The overall objective of the study was to determine if the device now known as the TAH-t (temporary Total Artificial Heart) was safe and effective for bridging patients to cardiac transplantation. 95 patients were enrolled (81 in the core implant group and 14, who did not meet study entrance criteria, but were treated under compassionate use and considered as an out-of-protocol cohort).

Treatment success was defined as patients who, at 30 days post transplant, were 1) alive; 2) New York Heart Association (NYHA) Class I or II; 3) not bedridden; 4) not ventilator dependent; and 5) not requiring dialysis. Overall survival, kidney and liver end organ function, and hemodynamics were secondary effectiveness endpoints.

Study inclusion criteria included: transplant eligibility; NYHA class IV; body surface area (BSA) 1.7-2.5 m^2 or distance between the sternum and 10^{th} anterior vertebral body, measured by CT scan, $\geq$ 10 cm; and hemodynamic insufficiency demonstrated by A or B below:

A: Cardiac index $\leq$2.0 l/min/M^2 and one of the following:
Systolic arterial pressure $\leq$90 mm Hg
Central venous pressure $\geq$18 mm Hg.

B: Two of the following:
Dopamine $\geq$10µg/kg/min
Dobutamine $\geq$10µg/kg/min
Epinephrine $\geq$2µg/kg/min
Isoproterinol $\geq$2µg/kg/min
Amrinone$\geq$10µg/kg/min
Other drugs at maximum levels
Intra-aortic balloon pump
Cardiopulmonary bypass

The 81 patients (referred to as the core group for the trial) met hemodynamic inclusion criteria as follows: 25 (30.9%) met A criteria (SAP<90 or CVP>18); 30 (37.0%) met B criteria (drugs, IABP, CVP); and 26 (32.1%) met both A and B. At study entry 15 patients were on cardiopulmonary bypass and 29 patients were supported by an intra-aortic balloon pump.

Exclusion criteria were:

- Use of any ventricular assist device
- Pulmonary vascular resistance $\geq$8 Wood (640 Dynes/sec/cm5)
- Dialysis in previous 7 days
- Serum creatinine $\geq$5 mg/dl
- Cirrhosis with bilirubin $\geq$5 mg/dl
- Cytotoxic antibody $\geq$10%.

Eligibility criteria needed to be met within 48 hours of implant.

A population for comparison was initially selected retrospectively from participating center records for a period during which the implant was not available, but subsequent review of their baseline data showed they were not comparable to the treatment group and statistically valid comparisons could not be made. As a result, a survival to transplant performance goal (65%) based on a literature search 1997 and later, that had been developed for univentricular devices, was used as a guideline. Adverse events for the trial participants and controls could not be compared to a performance goal due to differences in event definitions.

Study Population: The 81 patients in the core treatment group were 86% male and had an average age of 51 (range 16-67), an average weight of 85.3 kg, and a BSA of 2.0 m^2. All were NYHA class IV at enrollment. The etiology of the heart disease was 53% ischemic and 47% idiopathic.

Study Centers: Of the 5 centers participating in the study, 72% (58) implants were done at one site and 2 centers had 1 implant each. Two other centers implanted 13 and 8 patients, respectively.

The mean wait for a donor heart was 79 days with a median wait of 47 days. 64 of 81 core patients received transplants with a post transplant survival rate at 1 year of 85.9% and 5 year survival rate of 63.8%.

At 30 days post cardiac transplant, 56/81 (69.1%) of core patients met the five necessary criteria listed above to be considered a treatment success:

- 64 (79.0%) survived to transplant
- 58 (71.6%) survived to 30 days post transplant

Implanted core patients showed a number of improvements. Sixty-five percent were out of bed by the 5^{th} day and 60% could walk >100 feet by two weeks. Hemodynamically, on average, cardiac index improved 58% (from 1.9 L/min/m^2 to 3.0 L/min/m^2) and systolic blood pressure increased 32% (92.8 mm Hg to 122.7 mm Hg). Organ perfusion was calculated to have increased 42% and that increase was maintained during post operative monitoring. Hepatic and renal function normalized 3 weeks after implant. All 81 core patients received the CardioWest TAH-t.

Study Results:
Overall survival (81 patients):

- 6 months (75.3%)
- 12 months (70.4%)
- 24 months (67.9%)

Mean time to death or transplant: 79.1 days.

The average age of the 81 patient core treatment group was 51. Supplemental information supplied by the sponsor showed only one participant over age 65 years and that patient died 26 days after the implant while awaiting transplantation. Of 14 patients, aged 60 to 64 years, five died on the device, awaiting transplant. Of those in this age group transplanted (between 1995 and 2001) five were still alive as of October 31, 2006 when supplemental information was provided. One survived 5 years and 3 lived < 90 days.

Eleven of the 81 patients were female, ranging in age from 18 to 58. Two women died on the device, but six were still alive following transplant as of October, 2006. The sponsor advises that a total of 15 patients participating in the study (age range 36-64), including two women, were entitled to Medicare through entitlement to disability benefits and six of those patients were alive as of the date of submission of supplemental data.

We also were provided with supplemental information for fourteen additional patients who did not meet the criteria for entry into the IDE trial, but who received implants on a compassionate use basis because they were at imminent risk of death. One of these patients was 66 years old, was transplanted 4 months after receiving an implant and went on to live another year, but spent 154 days hospitalized between implantation and death. Five additional patients between ages 60 and 62 were included in this group. Three of those patients died on the device, one lived 17 days following transplant and one, transplanted in early 1996, remained alive as of October, 2006. There was one female patient in this compassionate use group, who died one day after implantation. Two of these patients (age range 34-60) were entitled to Medicare through disability.

Following the end of the IDE trial period, University Medical Center, Tucson, AZ, where the vast majority of implants had been performed, continued to do additional implants on transplant eligible patients. A group of 13 patients, who would have met the inclusion criteria if the study had been ongoing, were implanted between 10/03 and 03/06. One patient in the group was 63 years old and died on the device. The rest of the patients in the group were aged 15 to 59; three including a 59 year old died on the device. One patient died 3 months after transplant, and eight patients were alive as of October, 2006. There were no women in this group. Six of these patients (age range 32-63) were reported as entitled to Medicare.

Also, during the post study period, six additional patients, who would not have qualified for the trial, were implanted on a compassionate use basis. None of these patients was 60 years or over. Five died on the device and the only female patient in the group died one month after implant, on the day of transplantation. Three of these patients (aged 45-59) were reportedly entitled to Medicare.

FDA Panel Meeting

The FDA Circulatory System Devices Panel recommended approval of the TAH-t at a meeting on March 17, 2004 subject to the following:

1. A year long post market study and adding a contraindication that the device should not be used in patient in whom it would not fit.
2. A contraindication for patient who cannot receive anticoagulation therapy.
3. A warning that safety was not assessed in those patients who are not candidates for anti-platelet therapy.
4. Surgeons be required to view a human transplant with the device before attempting their own procedure.

Post-approval study protocol

The FDA approval letter issued April 9, 2004, required a post-approval study. Included with the SynCardia request for Medicare coverage of the TAH-t is a description of the FDA required post-approval study "to demonstrate that the results achieved in the original pivotal clinical investigation of 81 subjects from five clinical sites are generalizable to new clinical sites that complete the staff training defined in the SynCardia Systems, Inc. Training Manual and who enroll subjects who meet the intended use defined in the product Instructions for Use". Subsequent quotes in this section come from this submitted description.

Proposed Endpoints:

1. Efficacy:
    a. Subject survival at 30-days and one-year post transplant
    b. Transplant rates
    c. Time on device (implant to explant)
2. Safety
    a. Adverse events (INTERMACS definitions)
    b. Device malfunctions (failures and replacements will be documented)

This study is a "single-arm registry of transplant eligible patients who are at imminent risk of death as a result of hemodynamic deterioration. The study is designed to demonstrate that the safety and effectiveness of the TAH-t for use in bridge to transplant applications in newly trained clinical sites are comparable to the results obtained in the original pivotal trial." To eliminate bias, subjects receiving the TAH-t while the implanting surgeon is being proctored will not be included as part of the 50 subject cohort from new clinical sites. However, the identical information requested for the study will be collected.

Subjects will participate until one year after transplant. A baseline physiological assessment will be done before implant. Data related to blood products use and survival will be collected at implant and at explant. Survival data at 30 days (±7 days) and one year (± 30 days) post transplant will be collected. Neurocognative assessments will be done at baseline, 30 days post implant, 3, 6, and 12 months post implant and on the occurrence of a neurological adverse event.
One year post transplant SynCardia clinical personnel will telephone the subject directly. If the subject cannot be reached the transplant surgeon will be called or, if necessary, sent a registered letter to obtain follow-up information on the patient.

Inclusion Criteria:

1. Cardiac transplant eligible
2. At risk of imminent death from biventricular heart failure.

Exclusion Criteria:

1. Not cardiac transplant eligible
2. Insufficient space in the chest to accommodate the implant: body surface area <1.7m² or distance between 10th anterior vertebral body by CT scan <10 cm.
3. Cannot be adequately anticoagulated.

"The study protocol and the informed consent will undergo IRB [institutional review board] review to assure, both in advance and by periodic review, that appropriate steps are taken to protect the rights, safety and welfare of humans participating as subjects in the research. The IRB will monitor and review the progress of this post marketing study." A subject's consent to participate in the study will be sought "only under circumstances that provide the prospective subject or the representative with sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence".

Statistical analysis
Overall survival will be summarized using a Kaplan-Meier survival curve. Transplant and survival rates (at 30 days and one year) will be estimated along with 95% confidence intervals. The following data from the earlier study will be used as the basis for comparison:

Outcome	*Study result*
Transplant rate	79.0%
Survival at 30-days post transplant	71.6%
Survival at one year post transplant	70.4%

Mean time on device	79.1 days

As a comparison of efficacy:

Outcome	*FDA performance goal*	*Study result*
% survived to transplant	65%	79%
% survived 1 yr post transplant	NA	70.4%

Interim Reporting
The original study at five US centers took over 10 years to complete. Registry enrollment for the post-approval study began with the first subject at each of the next six clinical sites to complete the training protocol and was expected to take about 24 months. At 21 months into the study 38 patients have been registered in the US and of that group 19 have been transplanted, 12 have died and 7 are currently on the device awaiting organ donation. Ten centers have implanted at least one device, a total of 14 have been approved by the manufacturer to participate in the study and four additional sites are pending approval. Annual reports are prepared for the FDA, an interim report will be prepared when all 50 patients have been implanted and a final report when 50 patients attain one year post-transplant.

B. AbioCor Implantable Replacement Heart for destination therapy

The following discussion is based on the Summary of Benefit and Probable Safety for this device (H040006) found on the FDA website

(http://www.fda.gov/cdrh/pdf4/H040006b.pdf) with its Humanitarian Device Exemption (HDE) approval letter and other material and on supplemental material supplied by AbioMed in response to CMS request. The FDA approval permits implantation of up to 4000 devices annually in patients with severe end stage biventricular heart failure who are not transplant candidates and for whom therapeutic options have been exhausted. Also, it requires completion of a post-approval study of twenty-five patients which may be subject to FDA panel review after the first ten implants.

The AbioCor device is a pulsatile electrohydraulic implantable replacement for the native ventricles and their corresponding valves and most of the atria. It is sewn to the two atrial remnants and to grafts attached to the aorta and the pulmonary artery. The implant components can be thought of in two parts, internal and external:

- The internal thoracic unit weighs about two pounds and includes two artificial ventricles and a motor driven hydraulic pumping system; an electronics package that monitors and controls pump speed in response to physiologic demand; a rechargeable implanted lithium battery with a one hour life; and an energy transfer device (TET—transcutaneous energy transmission) which contains coils through which power is transferred from external TET coils. The internal implanted battery is continuously recharged via wireless transmission to the induction coil from external batteries;
- The external device components consist of a console which houses the systems monitor, the external portion of the TET system, lithium battery packs, which can power the device for up to four hours and a charger for the TET components and alarms. The portability of the battery packs and other external components allow the patient sufficient time to travel from the hospital to home or other locations and permit discharge so that he does not have to spend the balance of life confined to a hospital or other institution should his condition warrant.

The Summary of Safety and Probable Benefit for this device describes the study supporting its HDE approval. Implantation in up to fifteen subjects was approved with the condition that continuation beyond the first and second group of five patients was contingent on at least one patient in each group surviving at least 60 days without significant complications.

To be eligible for the study candidates must have been evaluated for possible cardiac transplantation and found not to be eligible, be in biventricular failure not treatable with an implantable LVAD, under optimal medical management, and unlikely to survive one month. Patients with irreversible end organ damage or inadequate psychosocial support were excluded. Candidates were also excluded if their prognosis for survival was >30% in the next 30 days based on clinical assessment of hemodynamic status, cardiac condition and end organ status. The potential for the device to fit the patient was assessed by MRI or CT scan as the device had to remain within the rib cage, while not interfering with the left bronchus and the left pulmonary veins.

Fourteen subjects were enrolled at 4 centers, with 12 at 2 of the centers. All were male, primarily due to fit constraints. Mean age was 67 (range 51 to 79) with 6/14 (43%) having been excluded from transplantation due to age. Other reasons for transplant exclusion included 4/14 (29%) due to irreversible pulmonary hypertension; 2/14 (14%) due to malignancy; and 2/14 (14%) due to multiple comorbidities including diabetes, neuropathy, renal dysfunction and hepatic dysfunction.

All patients were in NYHA class IV heart failure, primarily of ischemic origin (12 patients). Two patients had heart failure of unknown origin. All subjects were bed bound and the majority had previous cardiac device implants. Ten patients required intra-aortic balloon pump (IABP) support and 4 were on ventilator support. Primary comorbidities were pulmonary hypertension and renal dysfunction. The mean BSA (m^2) was 1.97 (range 1.72 to 2.24) and mean weight (kg) was 78.1 (range 60.8 to 96.3).

Preoperative hemodynamics data were collected within 2 weeks of implantation, but may not have represented the subjects' usual conditions, due to active support in anticipation of surgery. High levels of inotropic support (2.5 ± 1.0 drug types) were needed to maintain marginal cardiac output and systemic pressure.

Twelve subjects survived the implant surgery. Of the two subjects who did not survive surgery, one died of uncontrollable bleeding and one of pulmonary embolus. All four centers were successful with their first implant. The cumulative support duration for all subjects was 5.2 years. The mean individual survival time for all 14 patients was 4.5 months (range 0 to 512 days) while the median was 3.6 months. Ten patients lived longer than 60 days following implantation. Adverse events are summarized in Table 1.

Table 1: Adverse events in AbioCor study.

Type	# Subjects with event	Total # events
CVA	9	18
TIA (<24 hrs duration)	3	3
Non-surgical bleed	9	26
Surgical bleeding	10	42
Sepsis	2	2
Infection	11	33
Hepatic	6	7
Renal	9	8*
Respiratory	11	24

(*as reported on the FDA website)

The propensity to bleeding complications was attributed to the inability of 10 of 12 patients to tolerate the recommended level of anticoagulation (INR>2.5 or PTT>50 sec) more than 60% of the time and of these 10 patients 7 could not tolerate it more that 80% of the time.

None of the infections were considered device-related. Four subjects died of multi-organ failure or sepsis. One of the two septic events was a consequence of a massive abdominal bleed caused by a femoral vein puncture during a dialysis catheter exchange. The other resulted from a suture line which did not heal following surgery. Two additional deaths were the result of pre-existing hepatic dysfunction that failed to reverse.

In six patients, a cerebrovascular accident (CVA) led directly or indirectly to withdrawal of support with a mean time from event to withdrawal of 17.3 days. Three of these CVAs were due to inflow structure thrombus and three were due to factors preventing adequate anticoagulation.

There were two deaths attributable to device malfunction. In one case a membrane in the device wore out at 17 months and the subject declined a replacement device. A second subject died due to motor-bearing stoppage at 4.8 months.

Following implantation, cardiac output increased about 50%. Hemodynamic monitoring was continued only a short time after surgery to avoid complications from extended use of indwelling lines. In general, renal function as measured by creatinine levels improved over time. Serum bilirubin increased post-operatively, but normalized over one month.

Four patients had out of hospital activity after implantation. Two of these patients were discharged from the hospital—one to home and the other to a hotel near the hospital. In a effort to determine the impact of the device on patients' quality of life, the Minnesota Living with Heart Failure (MLWHF) tool was used both pre and post surgery. Some subjects were unable or unwilling to complete the questionnaire, resulting in no data being available for one subject and post implant data not being available for 4 additional patients. Of nine patients for whom post implant data was available, two recorded worsening scores.

FDA Panel Meeting

The FDA Circulatory System Device Panel met on June 23, 2005 to review the HDE application supported by the above study and did not recommend approval of the application. The Panel recommended that the sponsor maintain a Data Registry and form an Anticoagulation Management Committee to review the anticoagulation protocol and monitor the anticoagulation management of future device recipients.

FDA's Office of Device Evaluation in the Center for Devices and Radiological Health (CDRH) subsequently determined that this device met the HDE requirements in that it did not pose an unreasonable risk of illness or injury and that its probable benefit out weighed those risks when considering the risks and benefits of currently available devices or alternative forms of treatment.

In reaching this decision, three primary questions were considered:

- Is the device able to achieve the necessary level of circulatory support?
- Is the device sufficiently reliable?
- Does the device offer a probable benefit to patients and not pose an unreasonable risk of illness or injury?

FDA concluded that available data indicated that the device was able to achieve the desired level of circulatory support and that changes made in the device would improve its reliability and durability. Since there was no other approved destination therapy device for use in biventricular failure, this patient population had no other treatment options after optimal medical management proved insufficient. Further, the sponsor created the anticoagulation committee, which proposed a protocol that would be used in the post-approval study. Also the sponsor supplied additional information about subjects in the study confirming their biventricular failure and presented a robust set of factors that would be used to define biventricular failure in the post-approval study. AbioMed presented sufficient additional data about the incomplete quality of life information that FDA believed the results suggested that the device would be able to achieve a probable benefit in at least some implanted patients.

Because of the small number of patients in the clinical study on which this decision was based, FDA plans to present the results of the first ten patients from the post-approval study to the Circulatory System Devices Panel. This would allow for changes to the recommended clinical management of patients.

Post-Approval Study Protocol

This study is designed to verify that results in actual clinical use are similar to those observed in the previous study. The post-approval study will consist of at least 25 subjects treated in no more than 10 US heart centers. The first consecutive 25 patients who qualify under the selection criteria and have consented will be enrolled in the post-approval study. Among factors on which data will be collected in the study are patient selection, patient fit, surgery, post-operative management, ease of use and patient care. Adverse events to be followed will include frequencies of neurological events, infection, bleeding, renal dysfunction, liver dysfunction, thrombosis, and respiratory events.

Clinical parameters such as peak VO2 and 6 minute walks will be used to assess progress in rehabilitation. Duration of support, reversal and recovery of compromised organs, frequency of excursions outside the hospital, number discharged and activities of daily living upon discharge will be evaluated. Other factors to be considered in determining the value of the procedure to the patient will be length of stay, levels of care and re-admissions. Data related to anticoagulation management, nutrition, infection control, rehabilitation and patient activity will also be assessed.

A patient selection committee at each center with input from cardiac surgery, heart failure cardiology, hematology, neurology, infectious disease, pharmacy, psychiatry, nutrition, rehabilitation and social service will follow the HDE approved indications to select study subjects. A clinical coordinator and patient advocate will be available to the patient.

"A copy of the protocol and proposed Informed Consent form must be submitted to the IRB/IEC for written approval." "Patient informed consent is required for enrollment to ensure that patients are properly informed of the risks and potential benefits of the AbioCor System. Under the HDE, each Institutional Review Board (IRB) must approve the use of the AbioCor System at the respective center. A patient advocate affiliated with each center will be made available to an AbioCor candidate and his or her family to discuss options such as palliative care and the risks and potential benefits of the device. Prior to implantation of the AbioCor System, patients should discuss with family members and physicians the circumstances under which the device would be discontinued." Quotes in this section come from the protocol for the post-approval study, dated June 14, 2007, submitted by AbioMed to CMS.

Contraindications to study participation are:

- Presence of other irreversible end organ dysfunction that would compromise survival
- Inadequate psychosocial support
- Preoperative anatomical assessment indicating inadequate device fit
- Presence of coagulation disorders

To identify patients with likely coagulation problems those with severe liver dysfunction (as determined by liver biopsy) or bilirubin >3.5 mg/dL will be excluded. Patients with prothrombotic deficiencies or history of a GI bleed in the previous 3 months may be excluded after a full hematology consult.

A heart failure cardiologist will make the final determination that the subject is in chronic biventricular heart failure, using the following criteria:

- **Left-sided failure.** Elevated left atrial pressure ($\geq$ 18 mmHg.), low cardiac index ($\leq$ 2.2 L/min), and low LVEF ($\leq$ 20%) or CT/MRI evidence of distended left atrium (left atrial volume index $\geq$ 70 cc/m^2).
- **Right-sided failure.** Elevated right atrial pressure ($\geq$ 20 mmHg), or evidence of hepatic congestion of cardiac origin with a total bilirubin between 1.5 and 3.5 mg/dL, or CT/MRI evidence of distended right atrium (right atrial volume index $\geq$ 70 cc/m^2).

Screened patients found ineligible for the study due to fit failure or who refuse to consent to implantation will be monitored for survival at 30 and 60 days and at 6 months.

The AbioCor device's function is to provide hemodynamic support to the patient. Following implantation, numerous parameters including cardiac output, coagulation times, platelet function, patient volume status and nutritional condition will be monitored. Each implanting center will have an Anticoagulation Committee to oversee an individualized anticoagulation and antiplatelet strategy for each patient. Generally, each center will follow a protocol strategy using heparin anticoagulation followed by conversion to warfarin. Platelet therapy consisting of a combination of aspirin, dipyridamole, and clopidogrel bisulfate, when tolerated, will be initiated concurrently. Details of dosages and monitoring parameters are included in the approved protocol.

Other specific post implant care practices deal with infection management including prevention of nosocomial infections and supportive nutritional management. Adverse events will be reported using definitions used by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Routine quality of life measures including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the European Quality of Life instrument (EuroQoL) will be administered at baseline, monthly while hospitalized and, after discharge, quarterly or at a scheduled visit. Patients' activities and interactions will be documented daily while confined. Progress in physical rehabilitation and functional status will be recorded.

Neurological assessment will utilize the National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Scale (MRS) and cognitive function tests. The NIHSS and MRS will be performed pre-implant, weekly while hospitalized and quarterly following discharge. NIHSS obtained within 24 hours of an event will be considered a reasonable predictor of post hospital disposition. A score $\geq$14 likely would indicate need for nursing home care and >20 indicate a severe CVA.

The FDA approved protocol contains numerous details on treatment and data collection which are not included here, but which appear to assure that the study will achieve its goal of verifying that results at least comparable to the initial study on which HDE approval was granted can be achieved at other implanting sites.

4. Medicare Evidence Development and Coverage Advisory Committee

The committee was not convened for this topic.

5. Evidence Based Guidelines

CMS did not locate evidence based guidelines for the use of artificial hearts.

6. Professional Society Position Statements

CMS did not locate position statements on this topic.

7. Public Comments

In addition to requesting comments on coverage of artificial hearts for bridge to transplantation and destination therapy, the agency specifically requested that commenters discuss peer-reviewed, medical literature, hospital requirements (e.g., staffing, equipment) and surgeon and team training (e.g., proctoring, experience). CMS received 26 public comments during the initial 30-day public comment period. All commenters support the reversal of Medicare's noncoverage determination for artificial hearts with 21 commenters specifically supporting coverage of the CardioWest device for bridge to transplantation, three supporting the destination therapy indication with the AbioCor device, two with general support of Medicare coverage of artificial hearts and one against coverage of destination therapy.

Commenters pointed to public meetings held by the FDA and the FDA approval orders in addition to the following articles:

- Smith MC, Arabia FA, Tsau PH, Smith RG, Bose RK, Woolley DS, Rhenman BE, Sethi GK, Copeland JG. CardioWest total artificial heart in a moribund adolescent with left ventricular thrombi. Ann Thorac Surg 80(4):1490-2, 2005.
- Copeland JG, Smith RG, Arabia FA, Nolan PE, Sethi GK, Tsau PH, McClellan D, Slepian MJ. Cardiac replacement with a total artificial heart as a bridge to transplantation. N Engl J Med 351(9):859-67, 2004.
- Copeland JG, Smith RG, Arabia FA, Nolan PE, McClellan D, Tsau PH, Sethi GK, Bose RK, Banchy ME, Covington DL, Slepian MJ. Total artificial heart bridge to transplantation: A 9-year experience with 62 patients. J Heart Lung Transplant, 23(7):823-31, 2004.
- Copeland JG, Arabia FA, Tsau PH, Nolan PE, McClellan D, Smith RG, Slepian MJ. Total artificial hearts: Bridge to transplantation. Cardiol Clin 21(1):101-13, 2003.
- Copeland JG, Smith RG, Arabia FA, Nolan PE, Mehta VK, McCarthy MS, Chisholm KA. Comparison of the CardioWest total artificial heart, the Novacor left ventricular assist system and the Thoratec ventricular assist system in bridge to transplantation. Ann Thorac Surg 71(3 Suppl):S92-7, 2001.

These articles had also been cited by the requestor, but primarily deal with experience in using the TAH-t at the hospital which performed most of the implants of the SynCardia device. That information is well summarized in the material found on the FDA website and referenced in this decision.

Commenters stated that the following should be included in a training program: hands on training with animal models; post-operative mock loop training; lecture and discussion on best practices and experiences; and manufacturer proctored implantation. Commenters said the hospital team should be experienced in circulatory support and transplantation and the hospital should have a history of positive outcomes. Specifically, the team should include each of the following: surgeon; cardiologist; advance practice nurse; BSN nurse coordinator; operating room staff; perfusionist; clinical engineer; social worker; data collection staff; and finance and coding staff.

Commenters said artificial hearts could fill an unmet need in the Medicare population for patients with biventricular failure and no other treatment options. They said the currently reimbursed biventricular assist devices are inadequate compared to the high cardiac output attainable with artificial hearts. Other commenters stated that artificial hearts should only be covered for their FDA labeled indications and should not be reimbursed if used off-label.

Medicare coverage with study participation (Coverage with Evidence Development) was recommended by several commenters to allow access to the technology while data continues to be collected with one commenter recommending that the INTERMACS registry be the tool used for data collection. Another commenter suggested that future research trials are needed and should be developed with FDA, CMS and private insurers.

Comments were received regarding terminology. One commenter suggested that CMS eliminate the term "artificial heart" from coverage policy because the term does not clearly reflect the technology. It was suggested that artificial hearts should fall under the broader term of "mechanical assist for circulatory support" which would also include VADs. Further, the commenter recommended that coverage policy reflect a device's indication rather than device specifications (e.g., bridge to recovery, bridge to transplantation, destination therapy).

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

In addition to section 1862(a)(1)(A), a second statutory provision may permit Medicare payment for items and services in some circumstances. That statute, section 1862(a)(1)(E), provides, in pertinent part, that:
(a) Notwithstanding any other provision of this title, no payment may be made under part A or part B for any expenses incurred for items or services—
. . .
(E) in the case of research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section[.]
. . .

Section 1142 describes the authority of the AHRQ[2].

Under the authority of section 1862(a)(1)(E), CMS may pay for items and services furnished in connection with certain medical research. Coverage is conditioned on care being delivered in a setting with a pre-specified data collection process and additional protections in place such as are present in some research studies. Under section 1142, research may be conducted on the outcomes, effectiveness, and appropriateness of health care services and procedures to identify the manner in which diseases, disorders, and other health conditions can be prevented, diagnosed, treated, and managed clinically. In addition, evaluations of the comparative effects, health and functional capacity; alternative services and procedures utilized in preventing, diagnosing, treating, and clinically managing diseases, disorders, and other health conditions may be conducted.

In rare instances, for some items or services, CMS may determine that the evidence is very preliminary and not reasonable and necessary for Medicare coverage under section 1862(a)(1)(A), but, if the following criteria are met, CSP might be appropriate:

a. The evidence includes assurance of basic safety;
b. The item or service has a high potential to provide significant benefit to Medicare beneficiaries; and
c. There are significant barriers to conducting clinical trials.

These research studies will be rigorously designed and include additional protections and safety measures for beneficiaries.

To qualify for reimbursement, such a study must be designed to produce evidence that could be used in a future national coverage decision that would focus on whether the item or service should be covered by Medicare under 1862(a)(1)(A). Payment for the items and services provided in the study will be restricted to the Medicare qualified patients involved as human subjects in the study.

Consistent with section 1142 of the Social Security Act, AHRQ supports clinical research studies that CMS determines meet the above-listed standards and address the above-listed research questions.

In analyzing the evidence, CMS asked: "Is the evidence adequate to conclude that the artificial heart improves health outcomes in patients with end-stage, bi-ventricular heart failure?"

In our review, we evaluated two case series of artificial heart implantation. As noted in the Appendices, case series type studies provide limited evidence, in general, due to inherent methodological shortcomings. We did not find any randomized trials (published or presented) on the artificial heart. We did not find any study that compared the artificial heart concurrently to other treatments or optimal medical therapy. Neither the SynCardia nor AbioCor studies present sufficient evidence to support unrestricted coverage of artificial heart implantation.

In the case of the SynCardia TAH-t, a major weakness is the long period over which study implants were done and the paucity of data in recent years. The medical management of patients in biventricular failure has certainly improved in the 14 years since the first study patient was successfully bridged to transplant by this device. Also, from mid-2002 until mid-2006 all implants were performed at a single institution, thus raising the question of whether the device can successfully be implanted at additional institutions at this time. Fifty-eight of 81 (72%) implants in the pivotal trial and all thirteen implants performed under the continued access protocol were performed at University Medical Center in Tucson, AZ. Data from other institutions need to be collected in the post-approval trial.

The main weaknesses in the AbioCor study are the small number of patients implanted, that only one patient was discharged to home, that there were no women implanted and the relatively short period of support (mean 4.5 months) achieved prior to death. While one patient survived 17 months and was discharged to home, similar results need to be seen in other patients. The details of the post-approval protocol indicate major efforts to overcome the anticoagulation, bleeding and other problems encountered in the initial study. It is critical that these issues be addressed since adverse events occurred at high rates in the study, including the death of 6 patients directly or through withdrawal of support following a cerebrovascular event (CVA). Four other patients died of sepsis or multiorgan failure and device failure was the cause of two additional deaths.

One of our major concerns is the relatively few implanting hospitals and uneven distribution of patient experience among those hospitals in the studies. In addition, very few patients were enrolled in the destination therapy study (AbioCor) and the outcomes seen in the bridge to transplantation study (CardioWest TAH-t) are dated. CMS does not believe that the patient outcomes seen in these clinical studies can be extrapolated outside of the controlled, monitored clinical studies. Each study had weaknesses, which additional trials and continued device improvements are meant to address.

Several questions about the health benefits of an artificial heart not completely resolved on the basis of this evidence are:

- Were there unique circumstances such as expertise available in a particular facility or an unusual combination of conditions in particular patients that affected their outcomes?
- What will be the average time to device failure when the device is made available to larger numbers of patients?
- Do the results adequately reflect the full range of outcomes (both positive and negative) that might be expected from more wide spread use?

The FDA approved studies reviewed above and other such studies approved by the FDA may contribute to the current evidence base for artificial hearts and answer several of these questions. FDA approved studies have several important features that are designed to ensure the patient's likelihood of a good outcome, specifically the FDA review; patient selection criteria; facility selection criteria; clinician training; data collection, monitoring and reporting; and an analysis plan for evaluating the aggregate results. The studies also include features for patient protection that are uncommon in routine practice, such as the oversight by IRBs, use of a patient advocate, and discussions between the patient and family members about their goals of therapy.

IX. Summary

After reviewing the evidence, CMS believes that the evidence for the use of artificial hearts is promising. Therefore, CMS is proposing to cover artificial hearts when implanted under an FDA approved study when the study is designed to answer one of the above questions still remaining about the health benefits of artificial hearts and when the study meets the criteria detailed in Section I of this document.

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[1] Inotropes are vasoactive drugs used to improve cardiac output, blood pressure and urine output in heart failure.

[2] CMS has described this statute more fully in a Guidance Document available at https://www.cms.hhs.gov/ncpc_view_document.asp?id=8. See also section 310 Medicare National Coverage Determination Manual.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow -up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice. Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix B – Current policies from NCD Manual

20.9 - Artificial Hearts And Related Devices

A. General

A ventricular assist device (VAD) or left ventricular assist device (LVAD) is used to assist a damaged or weakened heart in pumping blood. These devices are used for support of blood circulation post-cardiotomy, as a bridge to a heart transplant, or as destination therapy.

B. Nationally Covered Indications

1. Postcardiotomy (effective for services performed on or after October 18, 1993)
Post-cardiotomy is the period following open-heart surgery. VADs used for support of blood circulation post-cardiotomy are covered only if they have received approval from the Food and Drug Administration (FDA) for that purpose, and the VADs are used according to the FDA- approved labeling instructions.

2. Bridge-to-Transplant (effective for services performed on or after January 22, 1996)
The VADs used for bridge-to-transplant are covered only if they have received approval from the FDA for that purpose, and the VADs are used according to the FDA-approved labeling instructions. All of the following criteria must be fulfilled in order for Medicare coverage to be provided for a VAD used as a bridge-to-transplant:
a. The patient is approved and listed as a candidate for heart transplantation by a Medicare-approved heart transplant center; and
b. The implanting site, if different than the Medicare-approved transplant center, must receive written permission from the Medicare-approved heart transplant center under which the patient is listed prior to implantation of the VAD.
The Medicare-approved heart transplant center should make every reasonable effort to transplant patients on such devices as soon as medically reasonable. Ideally, the Medicare-approved heart transplant centers should determine patient-specific timetables for transplantation, and should not maintain such patients on VADs if suitable hearts become available.

3. Destination Therapy (effective for services performed on or after October 1, 2003 with facility criteria updated March 27, 2007)
Destination therapy is for patients that require permanent mechanical cardiac support. The VADs used for destination therapy are covered only if they have received approval from the FDA for that purpose, and the device is used according to the FDA-approved labeling instructions.

Patient Selection
The VADs are covered for patients who have chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure for at least 90 days with a life expectancy of less than 2 years), are not candidates for heart transplantation, and meet all of the following conditions:
a. The patient's Class IV heart failure symptoms have failed to respond to optimal medical management, including dietary salt restriction, diuretics, digitalis, beta-blockers, and ACE inhibitors (if tolerated) for at least 60 of the last 90 days;
b. The patient has a left ventricular ejection fraction (LVEF) < 25%;
c. The patient has demonstrated functional limitation with a peak oxygen consumption of < 12 ml/kg/min; or the patient has a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion; and,
d. The patient has the appropriate body size ($\geq$ 1.5 m^2) to support the VAD implantation.

Facility Criteria
a. Facilities must have at least one member of the VAD team with experience implanting at least 10 VADs (as bridge to transplant or destination therapy) or artificial hearts over the course of the previous 36 months;

b. Facilities must be a member of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); and
c. By March 27, 2009, all facilities must meet the above facility criteria and be credential by the Joint Commission under the Disease Specific Certification Program for Ventricular Assist Devices (standards dated February 2007).

The Web site
http://www.cms.hhs.gov/MedicareApprovedFacilitie/VAD/list.asp#TopOfPage will be updated continuously to list all approved facilities. Facilities gaining Joint Commission certification (including prior to March 27, 2009) will be added to the Web site when certification is obtained.
Hospitals also must have in place staff and procedures that ensure that prospective VAD recipients receive all information necessary to assist them in giving appropriate informed consent for the procedure so that they and their families are fully aware of the aftercare requirements and potential limitations, as well as benefits, following VAD implantation.

C. Nationally Non-Covered Indications (effective for services performed on or after May 19, 1986)
1. Artificial Heart
Since there is no authoritative evidence substantiating the safety and effectiveness of a VAD used as a replacement for the human heart, Medicare does not cover this device when used as an artificial heart.
All other indications for the use of VADs not otherwise listed remain noncovered, except in the context of Category B IDE clinical trials (42 CFR 405) or as a routine cost in clinical trials defined under section 310.1 of the NCD manual (old CIM 30-1).

260.9 - Heart Transplants

A. General

Cardiac transplantation is covered under Medicare when performed in a facility which is approved by Medicare as meeting institutional coverage criteria. (See CMS Ruling 87-1.)

B. Exceptions

In certain limited cases, exceptions to the criteria may be warranted if there is justification and if the facility ensures our objectives of safety and efficacy. Under no circumstances will exceptions be made for facilities whose transplant programs have been in existence for less than two years, and applications from consortia will not be approved.

Although consortium arrangements will not be approved for payment of Medicare heart transplants, consideration will be given to applications from heart transplant facilities that consist of more than one hospital where all of the following conditions exist:

The hospitals are under the common control or have a formal affiliation arrangement with each other under the auspices of an organization such as a university or a legallyconstituted medical research institute; and

The hospitals share resources by routinely using the same personnel or services in their transplant programs. The sharing of resources must be supported by the submission of operative notes or other information that documents the routine use of the same personnel and services in all of the individual hospitals. At a minimum, shared resources means:

- The individual members of the transplant team, consisting of the cardiac transplant surgeons, cardiologists and pathologists, must practice in all the hospitals and it can be documented that they otherwise function as members of the transplant team; and
- The same organ procurement organization, immunology, and tissue-typing services must be used by all the hospitals; and
- The hospitals submit, in the manner required (Kaplan-Meier method) their individual and pooled experience and survival data; and
- The hospitals otherwise meet the remaining Medicare criteria for heart transplant facilities; that is, the criteria regarding patient selection, patient management, program commitment, etc.

C. Pediatric Hospitals

Cardiac transplantation is covered for Medicare beneficiaries when performed in a pediatric hospital that performs pediatric heart transplants if the hospital submits an application which CMS approves as documenting that:

- The hospital’s pediatric heart transplant program is operated jointly by the hospital and another facility that has been found by CMS to meet the institutional coverage criteria in CMS Ruling 87-1;
- The unified program shares the same transplant surgeons and quality assurance program (including oversight committee, patient protocol, and patient selection criteria); and
- The hospital is able to provide the specialized facilities, services, and personnel that are required by pediatric heart transplant patients.

D. Follow-Up Care

Follow-up care required as a result of a covered heart transplant is covered, provided such services are otherwise reasonable and necessary. Follow-up care is also covered for patients who have been discharged from a hospital after receiving a noncovered heart transplant. Coverage for follow-up care would be for items and services that are reasonable and necessary, as determined by Medicare guidelines. (See the Medicare Benefit Policy Manual, Chapter 16, "General Exclusions From Coverage," §180.)

E. Immunosuppressive Drugs

See the Medicare Claims Processing Manuals, Chapter 17, "Drugs and Biologicals," §80.3.1 and, Chapter 8, "Outpatient ESRD Hospital, Independent Facility, and Physician/Supplier Claims," §120.1.

F. Artificial Hearts

Medicare does not cover the use of artificial hearts as a permanent replacement for a human heart or as a temporary life-support system until a human heart becomes available for transplant (often referred to as a "bridge to transplant"). Medicare does cover a ventricular assist device (VAD) when used in conjunction with specific criteria listed in §20.9.

Appendix C – Proposed policies

20.9 - Artificial Hearts And Related Devices

A. General

A ventricular assist device (VAD) or left ventricular assist device (LVAD) *is surgically attached to one or both intact ventricles and* is used to assist a damaged or weakened *native* heart in pumping blood. *Improvement in the performance of the native heart may allow the device to be removed.*

An artificial heart is a biventricular replacement device which requires removal of a substantial part of the native heart, including both ventricles. Removal of this device is not compatible with life, unless the patient has a heart transplant.

B. Nationally Covered Indications

1. Postcardiotomy (effective for services performed on or after October 18, 1993)
Post-cardiotomy is the period following open-heart surgery. VADs used for support of blood circulation post-cardiotomy are covered only if they have received approval from the Food and Drug Administration (FDA) for that purpose, and the VADs are used according to the FDA- approved labeling instructions.

2. Bridge-to-Transplant

a. VADs as bridge-to-transplant (effective for services performed on or after January 22, 1996)
The VADs used for bridge-to-transplant are covered only if they have received approval from the FDA for that purpose, and the VADs are used according to the FDA-approved labeling instructions. All of the following criteria must be fulfilled in order for Medicare coverage to be provided for a VAD used as a bridge-to-transplant:
a. The patient is approved and listed as a candidate for heart transplantation by a Medicare-approved heart transplant center; and
b. The implanting site, if different than the Medicare-approved transplant center, must receive written permission from the Medicare-approved heart transplant center under which the patient is listed prior to implantation of the VAD.
The Medicare-approved heart transplant center should make every reasonable effort to transplant patients on such devices as soon as medically reasonable. Ideally, the Medicare-approved heart transplant centers should determine patient-specific timetables for transplantation, and should not maintain such patients on VADs if suitable hearts become available.

b. Artificial heart as bridge-to-transplant (effective for services performed on or after xx/xx/xx)
Implantation of the artificial heart for bridge-to-transplantation is covered only when furnished in accordance with the FDA-approved studies.

3. Destination Therapy

a. VADs as destination therapy (effective for services performed on or after October 1, 2003 with facility criteria updated March 27, 2007)
Destination therapy is for patients that require permanent mechanical cardiac support. The VADs used for destination therapy are covered only if they have received approval from the FDA for that purpose, and the device is used according to the FDA-approved labeling instructions.

Patient Selection
The VADs are covered for patients who have chronic end-stage heart failure (New York Heart Association Class IV end-stage left ventricular failure for at least 90 days with a life expectancy of less than 2 years), are not candidates for heart transplantation, and meet all of the following conditions:
a. The patient's Class IV heart failure symptoms have failed to respond to optimal medical management, including dietary salt restriction, diuretics, digitalis, beta-blockers, and ACE inhibitors (if tolerated) for at least 60 of the last 90 days;
b. The patient has a left ventricular ejection fraction (LVEF) < 25%;
c. The patient has demonstrated functional limitation with a peak oxygen consumption of < 12 ml/kg/min; or the patient has a continued need for intravenous inotropic therapy owing to symptomatic hypotension, decreasing renal function, or worsening pulmonary congestion; and,
d. The patient has the appropriate body size ($\geq$ 1.5 m^2) to support the VAD implantation.

Facility Criteria
a. Facilities must have at least one member of the VAD team with experience implanting at least 10 VADs (as bridge to transplant or destination therapy) or artificial hearts over the course of the previous 36 months;
b. Facilities must be a member of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS); and
c. By March 27, 2009, all facilities must meet the above facility criteria and be credential by the Joint Commission under the Disease Specific Certification Program for Ventricular Assist Devices (standards dated February 2007).

The Web site
http://www.cms.hhs.gov/MedicareApprovedFacilitie/VAD/list.asp#TopOfPage will be updated continuously to list all approved facilities. Facilities gaining Joint Commission certification (including prior to March 27, 2009) will be added to the Web site when certification is obtained.

Hospitals also must have in place staff and procedures that ensure that prospective VAD recipients receive all information necessary to assist them in giving appropriate informed consent for the procedure so that they and their families are fully aware of the aftercare requirements and potential limitations, as well as benefits, following VAD implantation.

b. Artificial Heart as destination therapy (effective for services performed on or after xx/xx/xx)
Implantation of the artificial heart for destination therapy is covered only when furnished in accordance with the FDA-approved studies.

C. Nationally Non-Covered Indications (effective for services performed on or after May 19, 1986)
All other indications for the use of VADs *or artificial hearts* not otherwise listed remain noncovered, except in the context of Category B IDE clinical trials (42 CFR 405) or as a routine cost in clinical trials defined under section 310.1 of the NCD manual (old CIM 30-1).

260.9 - Heart Transplants

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B. Exceptions

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E. Immunosuppressive Drugs

See the Medicare Claims Processing Manuals, Chapter 17, "Drugs and Biologicals," §§80.3.1 and, Chapter 8, "Outpatient ESRD Hospital, Independent Facility, and Physician/Supplier Claims," §120.1.

F. Artificial Hearts

Medicare covers ventricular assist devices (VAD) and artificial hearts when implanted under the coverage criteria stated in §20.9 of this manual (NCD Manual 100-03).

Back to Top